Replacement Drawing

Fig. 2 was objected to as being unreadable. A replacement Fig. 2 is submitted herewith in color. A petition to accept a color photograph under 37 C.F.R. § 1.84 is being concurrently submitted.

Attachment: Replacement Sheet

REMARKS

Amendments to the Claims

Claims 1-10 were pending.

Claims 11-13 have been added. Support for Claim 11 can be found in the Specification, for example, at page 8, lines 30-31; page 9, lines 11-12; page 25, line 30; and Fig. 1. Support for Claim 12 can be found in the Specification, for example, at page 9, lines 11-12. Support for Claim 13 can be found in the Specification, for example, at page 13, lines 28-31; and Figures 1-2.

Claim 8 has been amended to recite "a plurality of electrodes." Support for this amendment can be found in the Specification, for example, at page 13, lines 28-31; and Figures 1-2.

No new matter has been added. Entry of this amendment is respectfully requested.

Replacement Drawings

Fig. 2 was objected to as being unreadable. A high quality replacement Fig. 2 is submitted herewith in color to enhance the readability. A petition to accept a color photograph under 37 C.F.R. §1.84 is being submitted concurrently. No new matter has been added. Entry of the replacement Fig. 2 is respectfully requested.

Rejection of Claims 1, 2, 6 and 7 Under 35 U.S.C. § 102(b)

Claims 1, 2, 6 and 7 have been rejected under 35 U.S.C. §102(b) as being anticipated by Brown (U.S. Patent No.: 4,676,274; hereinafter, "Brown").

Claim 1

With respect to Claim 1, the Examiner stated that:

> ...Brown discloses a method of controlling the transfer of one or more liquid substances from a first cavity to the second cavity (e.g. 102 and 106 respectively of fig. 12) comprising introducing a fluid into a first cavity 102 whose transfer is to be controlled and holding said liquid in the first cavity which is connected to a second cavity 104 that is filled with a gas material that prevents

> transfer of liquid into the intermediate cavity…Brown further discloses that when the intermediate cavity is then vented, the gaseous separation medium is replaced with a liquid medium in the intermediate cavity (i.e., a connecting medium). The presence of this connecting medium thereby then allows fluid transfer from the first cavity to the second cavity owing to the removal of the liquid-air junction (col. 8, lines 22-32) (Office Action at page 3; emphasis added)

The rejection is based on a misinterpretation of the teachings of Brown. Brown's teachings are directed to controlling capillary flow of a principal fluid by controlling a control fluid (*see* Abstract; emphasis added). There are only two types of fluids involved in Brown's device and method. Unlike the present invention, Brown discloses neither a connection medium nor replacement of a separation medium with a connection medium as in the present invention. In Brown, release of pressurized air (*i.e.*, a separation medium) from the intermediate cavity allows the transfer of the principal fluid via reversing the potential energy states at the interface. For example, in one embodiment of Brown (col. 8, line 11 through col. 9, line 21; Figure 7) referred to in the Office Action (*see* Office Action at page 3), the presence of the control medium (*i.e.*, "air") prevents the flow of the principal medium (*i.e.*, "water") from a glass capillary tube 70 to a Teflon capillary tube 71. Pressurized air is, then, vented out, and this removal of the air results in removal of the liquid-air junction, allowing the capillary movement of the principal fluid from the glass tube 70 to the Teflon tube 71 (*see* Figures 9 and 10). Therefore, in Brown, it is the removal of the separation medium which automatically facilitates the transfer of the principal fluid, whereas the present invention involves replacement of the separation medium with a connection medium.

Brown simply does not teach any aspect relating to a connection medium. The movement of the principal fluid through the intermediate cavity is not "replacing" the separation medium with a connection medium. The movement of the principal fluid is the action of the transfer itself resulting from removal of the separation medium. Applicants wish to clarify that the principal fluid in Brown is the substance whose transfer is being controlled and cannot be construed as a connection medium as mistakenly suggested in the Office Action. The Brown reference does not anticipate the present invention directed to replacement of a separation medium with a connection medium which allows the transfer of the substances.

Claim 2

With respect to Claim 2, the Examiner stated that: "the embodiment of Figure 18 of Brown utilized the device for separating cells from a fluid using mechanical pumping" and cited col. 12, lines 23-60 of Brown. Notwithstanding the statement in the Office Action, Brown explicitly states that the device illustrated in Figure 18 is to be placed separately (*i.e.*, externally) from the main device (*see* Brown, col. 12, lines 23-30), indicating that the processing steps take place outside of the main flow system. Instant Claim 2, however, is directed to a method comprising the steps that are carried out *in* the first and/or second cavity. Thus, Claim 2 is not anticipated by Brown.

Claim 6

With respect to Claim 6, the Examiner stated that the device illustrated in Figure 12 of Brown anticipate the claimed device in Claim 6. As noted above, the intermediate cavity of Brown does not hold a connection medium, whereas the intermediate cavity of the present invention holds a connection medium. Therefore, the device shown in Figure 12 of Brown does not anticipate present Claim 6.

Claim 7

With respect to Claim 7, the Examiner referred only to the discussion for Claim 2. As noted above, Brown explicitly states that the device illustrated in Figure 18 is to be placed separately/externally. Instant Claim 7 recites that the mechanisms are placed in the first and/or second cavity. Thus, Claim 7 is not anticipated by Brown.

Rejection of Claims 1-10 Under 35 U.S.C. §103(a)

Claims 1-10 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Lee *et al.* (U.S. Patent publication 2002/0170825; hereinafter, "Lee") in view of Brown, with or without either Sundberg *et al.* (U.S. Patent No.: 6,090,251; hereinafter, "Sundberg") or Hochstrasser (U.S. Patent No.: 4,874,490; hereinafter, "Hochstrasser").

I. The Combined Teachings of Lee and Brown Do Not Render the Present Invention Obvious

With respect to Claim 1, the Examiner stated that: "It would have been obvious to one of ordinary skill in the art at the time the invention was being made to utilize an intermediate cavity between the first and second cavities (3 and 4) of the method of Lee so that the fluid flow between the two cavities is controlled until suitable transfer between the channels is so desired" (*see* Office Action at page 5).

Lee teaches a method and a device for two-dimensional electrophoresis. In Lee, samples are transferred from the first dimension cavities to the second dimension cavities by changing electric potential. Lee specifically teaches how to fill the first cavity and the second cavity with two different media (*i.e.*, step-wise filing of the two cavities as described in paragraphs [0043]; or placing a physical barrier such as a polymer membrane between the two cavities as in Figure 10 and paragraph [0044]). Because the first and the second cavities of Lee's micro-electrophoresis device are physically joined together in an orthogonal configuration (*e.g.*, Lee, Figure 1), Lee's device, as the Examiner correctly pointed out, does not contain the intermediate cavity. Nor does it include a separation or a connection medium to be held in the intermediate cavity. Because Lee's first and second cavities are already pre-filled with two different media as discussed above, transfer of samples from the first cavity to the second cavity is enabled by changing the electric potentials in Lee.

Brown teaches a method and device for controlling capillary movement of a principal fluid (*e.g.*, water) from one type of capillary tube to another. Brown teaches a method for controlling the movement of the principal fluid by applying and removing a control medium (*i.e.*, air). In Brown, removal of the control medium facilitates the movement of the principal fluid across the intermediate cavity. Brown's device does not include a connection medium, nor does it utilize replacement of a separation medium with a connection medium to enable the movement of a fluid.

The Combined Teachings of Lee and Brown Do Not Teach or Suggest the Present Invention

The combined teachings of Lee and Brown do not teach or suggest the use of a connection medium or a method of replacing a separation medium with a connection medium to facilitate the transfer from the first cavity to the second cavity. Lee is entirely silent on any

aspects relating to an intermediate cavity, separation medium, connection medium or replacement of the separation medium with the connection medium to allow transfer of the substance from the first cavity to the second cavity.

Brown's approach of controlling the movement of the principal fluid is different from the present invention. The movement of the principal fluid is controlled by placing one type controlling fluid (*e.g.*, the separation medium of air) in and out of the intermediate cavity. The movement of the principal fluid is achieved by differential capillary forces mainly created by the differences in surface materials and the surface energy between the surface material of the first cavity and that of the second cavity. Brown's teaching is limited to the use of only one controlling medium whose presence and absence is intricately intertwined with the surface energy of the principal fluid. Unlike Brown, the present invention utilizes active replacement of a separation medium with a connection medium that allows the transfer and the use of an intermediate cavity alternatively holding a separation medium and a conneetion medium. The combined teachings of Lee and Brown do not teach, suggest and render obvious the present invention.

One of Ordinary Skill in the Art Would Not Have Been Motivated to Arrive At the Present Invention with a Reasonable Expectation of Success

One of ordinary skill in the art reading Lee and Brown would not have been motivated to combine the teachings of Lee with the teachings of Brown to arrive at the present invention with a reasonable expectation of success.

But for impermissible hindsight, Lee's device for two-dimensional electrophoresis does not motivate one of ordinary skill in the art at the time of the invention to arrive at the present invention because Lee's device is designed to control the transfer of a substance from the first cavity to the second cavity by changing electric potentials between the first and the second cavities pre-filled with two distinct media with different electro-conductivities. Lee does not recognize or suggest any problem with the device. Nor does it motivate one of ordinary skill in the art to improve such device.

Further, Brown's device and method are silent on the use of a connection medium, and provides only limited teachings to the use of particular materials employed in making the first

and the second cavity in order to create differential capillary potentials. The capillary movement in Brown is actuated by releasing the pressurized control fluid / medium as discussed in detail above. One of ordinary skill in the art reading Lee and Brown would not have been motivated to combine or modify the teachings of Lee and Brown to arrive at the present invention.

With respect to Claim 1, the Examiner stated that: "Lee…does discuss that it would be desirable to control the filling of each of the cavities (i.e., microchannels) separately (*e.g.* par. 0043 and 0044)" (Office Action at page 4, final paragraph). Lee, however, does not explicitly state that it is desirable to control the filling. Lee provides a method of filling the cavities separately by either step-wise filling (*see* Lee, paragraph [0043]) or placing a physical barrier such as a polymer membrane between the first and the second cavities (*see* Lee, paragraph [0044]). Unlike the statement in the Office Action, one of ordinary skill in the art reading Lee would not have been motivated to implement a different method or improve the method and device taught in Lee because Lee already provides two methods for how to fill the cavities separately. But for impermissible hindsight, Lee's device does not motivate one of ordinary skill in the art to include an intermediate cavity directed to controlling the transfer of samples from the first cavity to the second cavity.

Further, Lee also discuss about placing a membrane barrier between the top substrate and the bottom substrate (*see* Lee, paragraph 44 and Fig.10) where a polymer membrane is placed to separate the top and bottom cavities, enabling one to fill the cavities with different media. Thus, Brown and Lee create different conditions in the first and second cavities by either filling them with different media as taught in Lee or creating the cavities with different surface materials to establish differential capillary potentials as in Brown. The present invention, however, provides a method of separating the cavity by providing an intermediate cavity and alternatively introducing a separation and connection medium into the intermediate cavity.

2. The Combined Teachings of Lee, Brown and Sundberg Do Not Render the Present Invention Obvious

Claim 1 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee in view of Brown and Sundberg. The Examiner stated that: "This use of Brown for Lee is further rendered obvious by Sundberg which teaches that the electrophoretic channels 78 might desire

different fluids than in the channel that 76 that feeds the electrophoretic channel. Sundberg suggests that a feature 90 be placed between these crossing channels such that fluid can be placed in one channel 78 without that solution bleeding into the crossing channel" (Office Action at page 5).

Deficiencies of Brown and Lee are discussed in detail above.

Sundberg provides an intermediate "region" designed to keep the first fluid in the first cavity from "wicking" into the second fluid in the second cavity. Sundberg specifically states that:

> To prevent the first fluid from filling the electroosmotic channel 76, a limit region 90 is disposed adjacent the junction of the two types of channels. Limit region 90 will have at least one cross-sectional dimension which is smaller than a cross-sectional dimension of the adjacent electroosmotic channel 76, the limit region ideally having a narrowest cross-sectional dimension which is smaller than the narrowest cross-sectional dimension of the electroosmotic channel. As a result, the first fluid will wick in to the limit region from electrophoretic channel 78, but differential capillary forces will prevent first fluid 86 from passing through limit region 90 and wicking into electroosmotic channel 76. The ratio of the minimum cross-sectional dimensions may again vary with the properties of the materials bordering the limit region and channels, with the limit region generally having a minimum dimension of less than 90% that of the channel. Typical electroosmotic and electrophoretic channel dimensions will be about 70 μm wide by 10 μm deep, while the corresponding limit regions may be about 70 μm wide by about 2 μm deep. (Sundberg, col. 9 line 51 through col. 10, line 3)

Similar to Brown, Sundberg teaches the use of an intermediate region (*i.e.*, "limit region 90") having a different cross-sectional dimension from the adjacent channels in order to create a differential capillary force between the first cavity and the second cavity. It is this capillary force that prevents the first fluid "wicking" into the second fluid in Sundberg. Like Brown, Sundberg does not disclose any aspects relating to a connection medium, or replacement of a separation medium with the connection medium whose presence triggers the movement of the substance. The teachings of Sundberg do not compensate the deficiencies in Lee and Brown. One of ordinary skill in the art would not have been motivated to modify or combine the teachings of Lee, Brown and Sundberg to arrive at the present invention because they do not

teach or suggest any aspects relating to the use of a connection medium and replacement of the separation medium with the connection medium.

3. The Combined Teachings of Lee, Brown and Hochstrasser Do Not Render the Present Invention Obvious

Claim 1 has been also rejected under 35 U.S.C. § 103(a) as being unpatentable over Lee in view of Brown and Hochstrasser. The Examiner stated that: "This use of Brown for Lee is further rendered obvious by the teachings of Hochstrasser which teaches an analogous two-dimensional electrophoresis experiment that it is desired to keep the first dimension experiment isolated from the second dimensional experiment by an electrically insulating layer that can be solid, liquid, or gas (col. 2, lines 22-39)" (Office Action at page 5).

It would not have been obvious to utilize the intermediate cavity of Brown between the first and second cavities (*i.e.*, microchannels) of the method of Lee because of the reasons discussed in detail above. Hochstrasser does not compensate for the deficiencies in Lee and Brown.

Hochstrasser teaches a system for two-dimensional gel electrophoresis, using two gels (*i.e.*, "strip gel" and "slab gel") separated by an insulating ("separation medium") layer that can be solid, liquid or gas (col. 2, lines 22-39). According to the teachings of Hochstrasser exemplified in Figure 3, the strip gel and the slab gel are separated by a space occupied by air. The first dimension of separation is permitted to occur on the strip gel with the present of air between the two gels. Once the desired separation is achieved in the first dimension, the two gels are placed in electrical contact for transfer from one gel to the other (col. 5, lines 3-24) either by: (1) pushing the first gel ("the strip gel") until it physically comes into contact with the second gel ("the slab gel") (*see*, col. 5, lines 25-30); or (2) introducing a new intervening gel between the first gel and the second gel (*see,* col. 5, lines 31-44).

Like Brown or Lee, Hochstrasser does not teach or suggest the use of a liquid connection medium to allow transfer of samples from the first cavity to the second cavity as set forth in the present invention. Hochstrasser does not motivate one of ordinary skill in the art to arrive at the present invention because, like Lee and Brown, Hochstrasser does not contemplate the use of a liquid connection medium as in the present invention.

Claims 2 and 3

With respect to Claims 2 and 3, the Office Action simply referred to paragraph 0040 of Lee. Paragraph 0040 of Lee teaches the use of a fluorescent dye to label protein samples in order to monitor the performance of isoelectric focusing in first dimension microchannels. However, Lee does not render Claims 2 and 3 obvious because Lee does not teach or suggest any aspects relating to the intermediate cavity, a separation medium or a connection medium. Even if the teachings of Lee is combined with the teachings of Brown, the teachings of Brown do not compensate for the deficiencies in Lee as discussed above.

Claim 4

With respect to Claim 4, the Examiner simple stated that: "Brown already teaches that the separation substance is air and the connection medium is whatever the fluid being placed in the connected microchannels (col. lines 22-32)" (Office Action at page 6). This statement is based on the misinterpretation the teachings of Brown. Brown does not teach or suggest any aspect relating to a connection medium whose present in the cavity allows the transfer of samples. Nor does Brown teach or suggest replacement of a separation medium with a connection medium. The Examiner mistakenly takes the principal fluid in Brown as a connection medium. As elaborated above, Brown teaches removal of the controlling fluid (*e.g.*, air) to allow the transfer of the principal fluid (*e.g.*, water) from one capillary tube to another. Simply, the movement occurs upon removal of the controlling fluid.

Claim 5

With respect to Claim 5, the Examiner stated that: "...Hochstrasser teaches that the electrical isolation can be provided by materials other than air such as fluids immiscible with the materials utilized for either of the first or second dimensional experiments (col. 4, lines 22-33)" (Office Action at page 6). The Office Action is based on a misinterpretation of Hochstrasser. Hochstrasser teaches that the protective layer (*i.e.*, separation medium) may be immiscible with either the gels or the gel-forming solution which merely supports the substances to be transferred (*see* Hochstrasser, col. 4, lines 28-31). Unlike Hochstrasser, the present invention is directed to a separation medium immiscible to the substance whose transfer is to be controlled. The teachings

of Hochstrasser is focused on separating the two gels, while the present invention is directed to controlling the movement of a substance from one cavity to another by controlling the medium in an intermediate cavity.

Claim 6

The Examiner stated that: "With respect to claim 6, as discussed in the previous 6/1/2009 Office Action, Lee discloses all limitations of the first cavity 3, second cavity 4, but does not explicitly teach the presence of intermediate cavity that connects the first and second cavities, but it would be desirable to control the filling of each of the cavities (*i.e.*, microchannels) separately (*e.g.*, paragraph 0043 and 0044)" (Office Action at page 6). The Examiner stated that there is a motivation to separate the fillings in the cavities as described in paragraph 0043 and 0044 in Lee and to utilize the intermediate cavity taught in Brown to achieve separate fillings.

Absent impermissible hindsight, one of ordinary skill in the art would not look to the teachings of Brown to arrive at the present invention because Lee teaches how to control the desired filling of each of the cavities separately. In Lee, the cavities are filled with different media in a sequential matter [0043] or separated by a physical barrier (*i.e.*, a polymer membrane) placed in between the top channels and the bottom channels as illustrated in Figure 10 (*see* also Lee, paragraph [0044]). With respect to the embodiment described in paragraph [0044] and Figure 10, placing membrane barrier B between the two substrates, A and C, is a logical approach for separating the two channels because the upper and bottom channels of Lee are physically enclosed in two different substrates (*see* Figure 10, items A and C). Generally, because the channels are filled with different media described by Lee, Lee achieves control of the movement of samples by simply applying different electric potential. Lee's teachings are complete and does not motivate one of ordinary skill in the art.

In addition, absent impermissible hindsight, one of ordinary skill in the art would not look to the teachings of Brown to arrive at the present invention because the characteristics of the intermediate cavity taught in Brown is largely different from the intermediate cavity set forth in present Claim 1. Brown's intermediate cavity is made out of a material which provides a different capillary potential from the first and second cavities in order to facilitate the transfer of the principal fluid upon removal of the control fluid. In contrast, the intermediate cavity of the

present invention is not bound by the characteristics of the intermediate cavity with respect to the capillary potential of the first cavity or the second cavity.

Even if the teachings of Lee are improperly combined with the teachings of Brown, the present invention is not achieved because Brown's intermediate cavity is different from that of the present invention in that the cavity described by Brown only facilitates the control fluid, whereas the intermediate cavity of the present invention alternatively facilitates the separation medium and a liquid connection medium, thereby enabling the movement of samples from the first cavity to the second cavity.

Because Lee controls the transfer of the fluid by preparing the first and second cavities filled with different media, for example, having a different electroconductive potential, while those of Brown is focused on creating cavities, including the first, second and intermediate cavities, with different materials in order to provide differential capillary forces in response to the presence and absence of the controlling fluid, one of ordinary skill in the art would have been motivated to combine the teachings of Lee with the teachings of Brown to arrive at the present invention.

Claim 7

With respect to Claim 7, the Examiner referred to the discussion of Claim 2. For the rejection of Claim 2, the Examiner referred to paragraph [0040] of Lee. Paragraph [0040] of Lee teaches the use of a fluorescent dye to label protein samples in order to monitor the performance of isoelectric focusing in first dimension microchannels. Claim 7 depends from independent Claim 6. As discussed above, Lee alone does not render present Claim 6 obvious, thereby failing render Claim 7 obvious.

Even if the teachings of Lee are combined with the teachings of Brown, the teachings of Brown do not compensate for the deficiencies in Lee as discusses above. One of ordinary skill in the art reading Lee and Brown would not have been motivated to combine the teachings of Lee with the teachings of Brown to arrive at the present invention with reasonable expectation of success.

Claim 8

With respect to Claim 8, the Examiner stated that: "the first cavity of Lee contains a first electrophoretic medium and second cavity contains a second electrophoretic medium..." However, Claim 8 recites the intermediate cavity, the element which Lee does not teach or suggest. Nor does Lee teach or suggest the use of a connection medium which allows the transfer of the substances.

Even if the Examiner combines the teachings of Lee with the teachings of Brown, the teachings of Brown do not compensate for the deficiencies in Lee because neither Lee nor Brown teaches or suggests a device holding a connection medium whose placement in an intermediate cavity allows the transfer of the substances. Further, Brown's mechanism for controlling the movement of the principal fluid is by placing one type control medium (*i.e.*, air) in and out of the cavity, whereas the present invention requires replacement of the separation medium with the connection medium to allow the transfer of the substance. Simply, the present invention solves a different problem from Lee or Brown. One of ordinary skill in the art reading Lee and Brown would not have been motivated to combine the teachings of Lee with the teachings of Brown to arrive at the present invention.

Claim 9

Claim 9 is directed to device in which the connection medium is introduced into the intermediate cavity via capillary action. The deficiencies in Lee and Brown are discussed above. Lee does not teach or suggest any device containing an intermediate cavity. Brown uses the capillary action for transferring the principal fluid whose movement is controlled by removal of air. Brown, however, fails to teach or suggest any aspects relating to the use of connection medium or delivery of such medium into the intermediate cavity. One of ordinary skill in the art would not have been motivated to modify the teachings of Lee and Brown to arrive at the present invention.

Claim 10

The deficiencies in Lee and Brown are discussed above. The Office Action is based on a misinterpretation of the teachings of Brown. Brown's teachings are directed to controlling

capillary flow of a principal fluid by controlling a control fluid (*see* Abstract; emphasis added). Brown discloses neither a connection medium nor replacement of a separation medium with a connection medium as in the present invention. In Brown, only one control fluid (*i.e.*, "air") functioning as a separation medium is disclosed. There, release of pressurized air from the intermediate cavity allows the transfer of the principal fluid via reversing the potential energy states at the interface. In Brown, it is the removal of the separation medium which facilitates the transfer of the principal fluid, not replacing the separation medium with a connection medium as in the present invention. The principal fluid in Brown is the substance whose transfer is being controlled, and cannot be considered as a connection medium as suggested in the Office Action. Therefore, the movement of the principal fluid through the intermediate cavity cannot be construed to constitute the action of "replacing" the separation medium with a connection medium. Therefore, Claim 10 is not rendered obvious over Lee in view of Brown.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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